CHARLES RIVER
LABORATORIES

March 13, 2007

Licensing Assistant Section
U.S. Nuclear Regulatory Commission, Region I
Commercial and R&D Branch
Division of Nuclear Materials Safety
475 Allendale Road
King of Prussia, PA 19046-1415

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RE: Associate RSO to be added to License Number 37-28306-01
Charles River Laboratories, Inc. – Malvern, PA
Docket Number 030-30892
~~Control No. 138227~~
140272

Dear Sir or Madam:

This letter is to notify the U.S. Nuclear Regulatory Commission that there have been some personnel changes at Charles River Laboratories, Biopharmaceutical Services (Malvern, PA). Additionally, we would like to amend our list of authorized supervisors of licensed materials (NRC Form 374, Section 12.)

Michael P. Silvon, Ph.D. is the new general manager of Charles River Laboratories, Biopharmaceutical Services, Malvern, PA (curriculum vitae included). Dr. Silvon replaces the previous general manager, Paula MacDonald.

Please remove Harvey R. Schlesinger, Ph.D., from the license. Dr. Schlesinger is no longer employed at this site.

Please add the following individuals as authorized supervisors to NRC Form 374, Section 12:

- Michael J. Hantman, Ph.D., has more than fifteen years of experience working with radionucleotides both in the academic and research biotechnology fields (curriculum vitae included).

- Brian P. Ruvolo, B.S., has more than five years of experience working with radionucleotides in the research biotechnology field (curriculum vitae included).

If you need additional information, please contact Douglas B. Brown, Ph.D., RSO, 610-640-4550 (extension 123) or Doug.Brown@pa.crl.com.

Sincerely Yours,

Douglas B. Brown, Ph.D., RSO
Charles River Laboratories, Inc.
Biopharmaceutical Services
358 Technology Drive
Malvern, PA 19355

cc: Michael P. Silvon, Ph.D.

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NMSS/RGN1 MATERIALS-002

MICHAEL P. SILVON, Ph.D.

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2006-present **CHARLES RIVER LABORATORIES, BIOPHARMACEUTICAL SERVICES (Malvern, PA)**
Biopharmaceutical testing business of $1 Billion revenue pharmaceutical research products and services provider. Global leader in animal models and preclinical research services. Report to President Preclinical Services Europe (Edinburgh, Scotland)

GENERAL MANAGER, Biopharmaceutical Services

- P&L for virology, molecular biology, process validation, microbiology, mycoplasma testing and related cGMP businesses.
- Chartered with responsibility to strengthen service, communications, timeliness, expertise and reliability among global clients.

1997-2006 **BIOANALYTICAL SYSTEMS, Inc. [BASi] (West Lafayette, IN)**
$40 million public company providing FDA compliant Contract Research Services and Instruments to the pharmaceutical industry. Report to Chairman/CEO. Recognized as a global knowledge leader in analysis of trace chemicals in biological fluids.

VICE PRESIDENT, Corporate Planning & Development

OPERATIONS
- P&L responsibility for $5 million preclinical toxicology/pathology research services business through 2003 till hand off to COO. Doubled staff to 70. Increased revenue >300%. (2000-03). Orchestrated construction project doubling capacity in 2002-03. Continued to own Business Development through 2005, further increasing revenue by 50% before hand off to new corporate sales team.
- P&L responsibility for Vetronics physiology monitoring instruments group. Launched Windows based veterinary diagnostic program, five new instruments, and successful key account program.

DEVELOPMENT
- Created and implemented acquisition strategy – five GXP acquisitions (Phase I/IIa human clinical trials, preclinical lab, US & UK based bioanalysis labs, veterinary diagnostic instruments) completed since 1997. Responsible for integrating acquired companies.

FINANCE
- Interim CFO 11/03 through 3/04. Worked with outside accounting consulting firm. Completed year-end audit. Compiled and filed SOX compliant SEC reports. Renegotiated bank covenants. Recruited new CFO and Controller. Refinanced company through investment banking consultants with three bank syndicate (2003)
- Orchestrated $6.5 Million sale/leaseback of Baltimore Clinical Research facility (2005).

CORPORATE
- Compiled and communicated BASi corporate business plan.
- Assistant Secretary to the BASi Board of Directors. Chair SOX Compliance Disclosure Committee.
- Responsible for corporate Investor Relations [full disclosure, relationship with NY based IR firm, road show presentations, analyst relations, banking relationships, and internal materiel development].
- Broadened corporate network through state life science initiatives, banks, venture capitalists, universities, etc. in Indiana, Baltimore and Philadelphia
- Member BASi Initial Public Offering team, 11/97.
- Advisor/consultant to Sentry Logistics (GMP, biopharmaceutical cold storage venture) Green Mountain Logics (GXP services management software) and others (2006)

1996-Present **PALANTEK CONSULTING, LLC** - *PRINCIPAL*
Private consultant. Completed short-term assignments (market studies, business planning, technology management) for technically driven organizations marrying good business practices to good science.

1993-1995 **HI-PORT, Inc. (Houston, TX)**
$17 million revenue 1990 LBO specializing in formulation, packaging, warehousing and distribution of agrochemical and specialty chemical products to retail and industrial markets. Recognized nationally for leadership in Quality. Reported to President/CEO.

VICE PRESIDENT, Sales & Marketing

- Directed worldwide sales & marketing. Created client oriented development program that exploited distinguishing corporate characteristics, [Quality, ISO9002, employee empowerment, and automation]; introduced seven new products in first year generating > $2 M/annum margin.
- Played key role with board and investors in development of strategic/tactical business plan and focused growth through acquisition. Assessed multiple candidates.

1987-1993 **ICI AMERICAS / ZENECA (Wilmington, DE)**
$5 Billion division of $20 billion UK based, multinational manufacturer of basic, specialty and performance chemicals. Reported to Fine Chemicals Business General Manager (Manchester, UK)

REGIONAL BUSINESS MANAGER - Fine Chemicals

- P&L Responsibility. Led North/South American marketing and sales. Consolidated five chemical business sectors into single $62 million territorial business unit.
- Merged former Stauffer Intermediates group into new, global fine chemicals business (agricultural/pharmaceutical) creating >$100 million/year ICI Fine Chemicals. Integrated U.S. view into global strategy as business team member.
- Upgraded and directed new product development. Three new products valued at $6M/annum.
- Shared responsibility for $22 million fixed cost budget at two plants. Optimized cash generation from manufacturing assets ($7 million/year) by maximizing capacity utilization and developing new, low-capital products.

1976-1986 **STAUFFER CHEMICAL COMPANY (Westport, CT)**
$1.5 billion manufacturer of specialty and basic chemicals.

1981-1986 *BUSINESS MANAGER & MANAGER, Commercial Development – Intermediates*

- P&L for of $42 million/annum sales among 30 global clients.
- Created global growth strategy expanding intermediates sales outside of U.S. by 200% to $12M.
- Created and ran product development pipeline. Screened 100 products/year resulting in ten commercial products. Managed $2 million research effort to ensure a cost and time efficient, market oriented program.

1976-1980 *SENIOR RESEARCH CHEMIST & TECHNOLOGY PLANNING ASSOCIATE*

EDUCATION & PROFESSIONAL

1985	Sacred Heart University (Fairfield, CT)	M.B.A
1973	University of Vermont (Burlington, VT)	Ph.D. Physical Organic Chemistry
1969	Loyola University of Chicago (Chicago, IL)	B.S. Chemistry

Postdoctoral Fellowships:

1975	Organometallic Chemistry, Fellow, Alexander von Humboldt Foundation – Tech. Univ. of Munich
1974	Organometallic Chemistry, Pennsylvania State University (State College, PA)

Professional:

2001-present	Drug Information Association
2001-present	Society of Toxicology, Associate Member
1999-present	American Association of Pharmaceutical Scientists
1969-present	American Chemical Society, Chairman, Purdue University Local Section (1999-2005)
1971-present	American Association for the Advancement of Science
1981-1993	Drug, Chemicals and Allied Trades Association, Board of Directors (1992-93)

Michael J. Hantman, Ph.D.

[redacted]

610-640-4550 (Work)

[redacted]

michael.hantman@PA.CRL.com

Education

1994	Temple University School of Medicine Ph.D., Department of Microbiology and Immunology	Philadelphia, PA
1977	Temple University B.A., Department of Biology	Philadelphia, PA

Research Experience

2005-Present — Charles River Laboratories, Biopharmaceutical Services — Malvern, PA

Associate Director of Methods Development

In my role as Associate Director of Methods Development, I direct the activities of a scientific group in the research and development of new molecular assays, in the improvement of existing assays and in the transfer and execution of client/sponsor-directed assays. Over forty new assays have been developed within the parameters of a GMP environment. The primary focus is on molecular assays for detection and identification of adventitious or contaminating agents including bacteria, mycoplasma, yeast, and viruses. PCR-based protocols have been expanded to include residual DNA determination and cell line characterization including gene copy number determination, DNA sequencing of recombinant genes and DNA sequencing for species identification. In addition to generating new assays, methods development is involved in improving existing assays by increasing sensitivity, decreasing turnaround time, and decreasing costs. The methods development group has interacted with other departments to successfully implement newly developed assays and cooperated with other departments to succeefully complete multi-assay studies for customers.

As Associate Director, I have developed strategies to ensure effective achievement of scientific objectives, I have monitored and evaluated completion of tasks and projects and have participated in budget development for capital expenditures and labor. In addition, my responsibilities include generation of standard operating procedures, standard test methods, and qualification protocols for the validation of the performance of each new assay within ICH and FDA guidelines. I have also assisted the company's sales and marketing efforts by any number of the following activities: discussions of assay procedures with present and potential customers, travel with sales personnel, publications, seminar presentations, tradeshow attendance.

2000-2005 — Charles River Laboratories, Biopharmaceutical Services — Malvern, PA

Assistant Director of Methods Development

My role as Assistant Director of Methods Development has involved design, experimentation and implementation of new testing procedures to expand the range of assays performed at Charles River Laboratories.

Responsibilities also included management of day to day operations, assay qualification and training of managers, supervisors and technicians and troubleshooting any technical and scientific problems arising in the laboratories. In addition, I have been involved in the preparation of related documents necessary for implementation of newly developed assays as well as updated, improved existing assays. Equally important are the day to day support of the sales and customer service staff and the provision of excellent service to our customers.

1995-2000 University of Washington, Department of Microbiology and Immunology, Seattle, WA

Research Fellowship

Vaccine development using antigens delivered by bacterial systems: Use of a type III secretion system in attenuated Salmonella typhimurium and Salmonella typhi strains to translocate fusion proteins, created by ligation of effector protein genes and various heterologous antigen coding sequences, into the mammalian cell cytosol. This antigen presentation system is designed to generate both MHC class I and MHC class II responses. Tested the effect of timing of translocation on the immune response by swapping effector protein domains, which utilize either pathogenicity island I or II secretion/translocation systems.

Mammalian host responses to subsets of bacterial proteins: One of the important questions in these studies is to discern the role of individual effector proteins in down-regulating the host immune response. The antigen presentation system using fusion proteins will aid the functional analysis of bacterial proteins during infection. Tested the effect of mutation of potential virulence determinants, including PhoP, a transcriptional regulator, SptP, a protein with tyrosine phosphatase and GAP (GTPase activating protein) activities and SspA (SipA), an actin-binding protein.

Assist in training of graduate students.

1993-1995 Harvard University, Department of Medicine, Massachusetts General Hospital, Infectious Disease Unit, Boston, MA

Research Fellowship

Identification of Salmonella secreted proteins affecting mammalian host functions: Optimized conditions to isolate and purify secreted proteins from various Salmonella strains. Produced high affinity antibodies to several secreted proteins.

Genetic analysis of Salmonella pathogenicity islands: Sequenced virulence determinants within Salmonella pathogenicity island I, produced and tested insertional or deletional mutations for virulence associated phenotypes and subcloned sspA (sipA) and sptP to analyze its secretion/translocation properties and enzymatic activities.

1989-1994 Temple University School of Medicine, Department of Microbiology and Immunology, Philadelphia, PA

Graduate Student

Genomic mapping of Streptococcus mutans: Developed methodologies to isolate intact chromosomal DNA from Gram-positive bacteria, necessary for optimal low frequency restriction enzyme digestion and resolution of very large DNA fragments by pulsed-field gel electrophoresis. Produced the first physical map of the S. mutans genome using overlapping restriction fragments and mapped over fifty genes including all the known virulence determinants and the rRNA operons. Utilized transposon Tn916 to mark fragments by shifting their mobility, thus allowing fragments generated by different enzymes to be aligned.

Analysis of virulence determinants from Streptococcus mutans: Cloned and sequenced glucosyltransferases and studied the effect of expression in heterologous streptococcal backgrounds. Teaching assistant for Medical Microbiology labs.

1978-1989 Temple University School of Medicine, Department of Microbiology and Immunology, Philadelphia, PA

Technician

Analysis of virulence determinants from Streptococcus mutans.

Techniques

Radioisotopes: Extensive training in the safe handling and use of radiolabeled materials.

DNA: Purification and analysis including cloning, sequencing, mutagenesis, deletional analysis, pulsed-field gel electrophoresis, Southern blot analysis with both radioactive and nonradioactive probes, transcriptional and translational fusions.

RNA: Northern blot analysis, sequencing.

PCR and RT-PCR: Real time qualitative and quantitative PCR and RT-PCR using fluorescence-based detection systems and fluorogenic probes as well traditional methods.

Protein: Purification and analysis of proteins from Gram-positive and Gram-negative bacteria and mammalian cells, including PAGE, zymography, Western blot analysis, ELISA, kinase/phosphatase assays, beta-galactosidase assays and bacterial expression of tagged fusion proteins.

Cell Culture: Isolation, cultivation and biochemical analysis of both primary mammalian cell cultures (bone marrow-derived macrophages, PBMCs, splenocytes) and cell lines (including transformed T cells, B cells, macrophages, dendritic cells, epithelial cells). Analyses include bacterial invasion of eukaryotic cells, cytotoxicity, cAMP levels and microscopy.

Immunoassays: Antigen presentation assays, including ELISAs and tritiated thymidine uptake, detecting increases of interleukin levels in splenocytes and T cell cultures and T cell proliferation following stimulation with experimental APCs, and chromium release for cytotoxic T cell activity.

Confocal microscopy in conjunction with immunofluoresence.

Antibody Production and Purification: Rabbit and mouse.

Familiarity with Sample Trak, Microsoft Word, Excel, PowerPoint as well as DNA analysis tools including GCG, Sequencher, Lasergene, Applied Biosystems Sequencing Analysis software, Primer Express and NCBI databases.

Publications

M. J. Hantman, E. L. Hohmann, C. G. Murphy, D. M. Knipe, S. I. Miller. (1999) Antigen delivery systems: Development of recombinant live vaccines using viral or bacterial vectors, p. 779-791. In, Mucosal Immunology. eds. P. L. Ogra, et al., 2nd ed. Academic Press, San Diego.

C. A. Scherer, M. J. Hantman, S. I. Miller. (1997) Salmonella invasion and delivery of protein effectors to mammalian cell cytoplasm. Trends in Microbiol. 5:127-129.

C. J. Hueck, M. J. Hantman, V. Bajaj, C. Johnston, C. A. Lee, S. I. Miller. (1995) Salmonella typhimurium secreted invasion determinants are homologous to Shigella Ipa proteins. Mol. Microbiol. 18:479-490.

D. A. Pegues, M. J. Hantman, I. Behlau, S. I. Miller. (1995) PhoP/PhoQ transcriptional repression of Salmonella typhimurium invasion genes: evidence for a role in protein secretion. Mol. Microbiol. 17:169-181.

R. M. Tsolis, L. G. Adams, M. J. Hantman, C. A. Scherer, T. Kimbrough, R. A. Kingsley, T. A. Ficht, S. I. Miller, A. J. Baumler, (2000) SspA is required for lethal Salmonella enterica serovar Typhimurium infections in calves but is not essential for diarrhea. Infect Immun. 68:3158-3163.

M. G. Capiello, M. J. Hantman, F. M. Zuccon, F. Peruzzi, M. Amjad, P.J. Piggot, L. Daneo-Moore. (1999) Physical and genetic map of Streptococcus mutans GS-5 and localization of five rRNA operons. Oral Microbiol. Immunol. 14:225- 232.

M. J. Hantman, S. Sun, P. J. Piggot, L. Daneo-Moore. (1993) Chromosome organization of Streptococcus mutans GS-5. J. Gen. Microbiol. 139:67-77.

M. J. Hantman, J. J. Tudor, S. Sun, L. Marri, P. J. Piggot, L. Daneo-Moore. (1991) Physical and genetic mapping of the Streptococcus mutans GS-5 genome, p.289. In, Genetics and Molecular Biology of Streptococci, Lactococci, and Enterococci. eds. G. D. Dunny et al., ASM, Washington.

S. Sun, L. Daneo-Moore, L. Marri, M. J. Hantman, G. D. Shockman. (1991) Genetic and physiological studies of variants of Streptococcus mutans GS-5 that produce nonmucoid colonies on sucrose-containing media, p.256-260. In, Genetics and Molecular Biology of Streptococci, Lactococci, and Enterococci. eds. G. D. Dunny et al., ASM, Washington.

References

Available upon request

Brian Peter Ruvolo

Office Address:
Charles River Laboratories
358 Technology Drive
Malvern, PA 19355
Brian.Ruvolo@pa.crl.com
(610)-640-4550 ext. 188

Home Address:
[redacted]

SUMMARY OF QUALIFICATIONS

Experienced Molecular Biologist with expertise in a variety of Molecular-based assays; including the determination of residual DNA levels in samples by means of hybridization, the characterization of DNA utilizing various techniques, QF PCR, Microbial Cell Banking, and numerous methods used in cellular characterization.

- Skilled in guiding experiments through all phases of testing from initiation to completion, and identifying any additional experiments necessary to achieve research and testing objectives.
- Trained in leading other technicians and co-workers in all aspects of the laboratory, from developing specific assays and procedures to completing these assays and analyzing the data.

EDUCATION

West Chester University, PA. **Master's Degree**, Biology (In progress) **2005 - Current**

West Chester University, PA. **Bachelor's Degree**, Cell and Molecular Biology **2000**

PROFESSIONAL EXPERIENCE

Supervisor, Molecular Biology: Charles River Laboratories **2001 – Current**

Became an employee of Charles River Laboratories in 2001 as a Technician. While employed, I was internally promoted to Senior Technician, Team Leader, and most recently to Supervisor of the Molecular Biology Department in June of 2004.

Essential Duties and Responsibilities:

- Supervise daily laboratory activities and laboratory scheduling.
- Supervise the use of radioactive materials in the laboratory, and ensure their proper handling, storage, and disposal.
- Train technical personnel in laboratory skills and techniques, and reinforce regulatory concepts (cGMP).
- Perform technical troubleshooting, develop assays that meet regulatory guidelines, and validate new assay formats as well as re-evaluate existing assays.
- Revise existing documents to ensure the laboratory maintains its compliance status.
- Develop new protocols for client-specific assays.
- Develop and administer schedules and performance reviews.
- Provide direct daily supervision and review work of assigned departmental employees to ensure accuracy and adherence to pertinent departmental policies, practices, and procedures (SOP's, safety procedures, and biosafety protocols). Schedule and prioritize workload of group members.
- Assist in the interview and selection of qualified non-exempt personnel. Recommend personnel actions, including hiring, promotions, and raises.
- Identify training and development needs of direct reports. Assist in the development, implementation, and delivery of departmental training programs; ensure that direct reports receive departmental orientation and necessary on-the-job training. Oversee maintenance of group training manual and training records.

- Monitor performance of direct reports. Provide regular coaching and counseling. Assist in preparation and delivery of salary and performance reviews of direct reports.
- Schedule overtime as authorized. Review and approve time cards. Coordinate vacation/time off schedules.
- Recommend short-range operating objectives, organizational structure of direct reports and staffing requirements. Assist in the development of a departmental plan for backup and succession of key technical personnel.
- Ensure optimum performance of group function. Recommend and implement techniques to improve productivity, increase efficiencies, cut costs, take advantage of opportunities, and maintain state-of-the-art practices.
- Assist in the development, maintenance, and communication of departmental systems and SOP's. Assist in the development and communication of job descriptions for subordinate positions.
- Ensure that departmental equipment is maintained in good working condition and that departmental area(s) are maintained in a clean and orderly condition.

TECHNICAL EXPERTISE

Generation of competent cells for transformation
Transformation of chemically competent bacterial cells
DNA ligation reactions and cloning
Purification of plasmid DNA propagated in bacterial hosts
Extraction of viral DNA
Extraction of genomic DNA from mammalian, yeast, and bacterial cells in culture
Agarose gel electrophoresis
Purification of DNA fractionated on agarose gels
Digestion of DNA with restriction enzymes and subsequent analysis
Preparation of radiolabeled DNA probes
Preparation of fluorescent dye-labeled probes
Southern blotting
Hybridization of radiolabeled probes to immobilized nucleic acids
Amplification of DNA using the polymerase chain reaction
Quantitative fluorescence PCR
Analysis of gene copy number
Microbial culture growth and cell banking techniques
Microbial colony replica plating
Analysis of growth techniques
Microbial gram staining
Light microscopy
Determination of the retention of a selectable marker by a host cell line
Determination of the retention of a recombinant construct by a host cell line
Determination of the viability of a microbial culture
Determination of the purity of a microbial culture
Plaque Analysis

REFERENCES

- Available upon request.

This is to acknowledge the receipt of your letter/application dated

3/13/2007, and to inform you that the initial processing which includes an administrative review has been performed.

☑ AMDT. 37-28306-01
There were no administrative omissions. Your application was assigned to a technical reviewer. Please note that the technical review may identify additional omissions or require additional information.

☐ Please provide to this office within 30 days of your receipt of this card

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A copy of your action has been forwarded to our License Fee & Accounts Receivable Branch, who will contact you separately if there is a fee issue involved.

Your action has been assigned **Mail Control Number** 140272.
When calling to inquire about this action, please refer to this control number.
You may call us on (610) 337-5398, or 337-5260.

NRC FORM 532 (RI)
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Sincerely,
Licensing Assistance Team Leader